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REVIEW article

Molecularly targeted theranostics in neurology and neuroinflammation: Current status and future directions

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Abstract: By combining imaging and targeted therapy into a single platform, theranostics, an emerging field in neurological diseases, has the potential to completely transform diagnosis and treatment. Alzheimer's disease, Parkinson's disease, multiple sclerosis, glioblastoma, epilepsy, and other neurological conditions pose a number of complex challenges, such as difficulties in early diagnosis, restrictions in the delivery of drugs across the blood-brain barrier, and a lack of real-time therapeutic monitoring. Molecular imaging methods, such as PET and MRI, are utilized in theranostic approaches, along with drug delivery systems based on nanotechnology that can cross the blood brain barrier. Functionalized nanoparticles improve personalized medicine by enabling accurate targeting and concurrent imaging and treatment. Amyloid-PET tracers and therapeutic agent-loaded nanocarriers are two disease-specific theranostic approaches that have shown promise in preclinical and clinical research. For increased accuracy and effectiveness, future directions focus on combining state-of-the-art technologies, such as artificial intelligence and CRISPR-Cas9 gene editing. Theranostics holds revolutionary potential for managing neurological disorders by enabling early detection, personalized therapy, and dynamic treatment monitoring, despite translational challenges related to blood-brain barrier penetration, safety, regulatory barriers, and cost. To advance clinical outcomes in neurology and move these innovations from the bench to the bedside, more interdisciplinary research is essential.

Introduction

Neurological diseases, from Alzheimer's to glioblastoma, are among the most intricate and debilitating medical illnesses in the world [1]. Efficient treatment of the diseases is normally hampered by the lack of early diagnosis, poor drug delivery across the blood-brain barrier (BBB), and insufficient real-time monitoring systems. Theranostics offers a double solution through the simultaneous integration of diagnostic imaging and targeted therapy in one platform, which allows for personalized and effective disease management [2]. Neurological diseases are a group of pathological conditions involving the central and peripheral nervous system. The heterogeneity and complexity of neurological diseases pose a lot of problems for clinicians and researchers. Conventional diagnostic methods are not very specific, and therapeutic maneuvers can be hindered by delayed diagnosis or nonspecific targeting [3]. Theranostics overcomes the above limitations by combining

diagnostic and therapeutic functions into one system. This union enables superior detection, customized treatment strategies, and dynamic monitoring of therapeutic response. In neuroscience, the method is especially useful owing to the brain's specific microenvironment and the existence of the BBB, which prevents most drugs from accessing target sites. Neurology has seen a great advancement in theranostic applications because of interdisciplinary advancements in nanomedicine, molecular biology, and neuroimaging. Such systems are now able to identify early pathological alterations and treat the concerned brain areas with specific treatment [4]. This review integrates available literature on existing advancements in theranostic methods across prevalent neurological diseases and highlights clinical usage and future approaches [5].

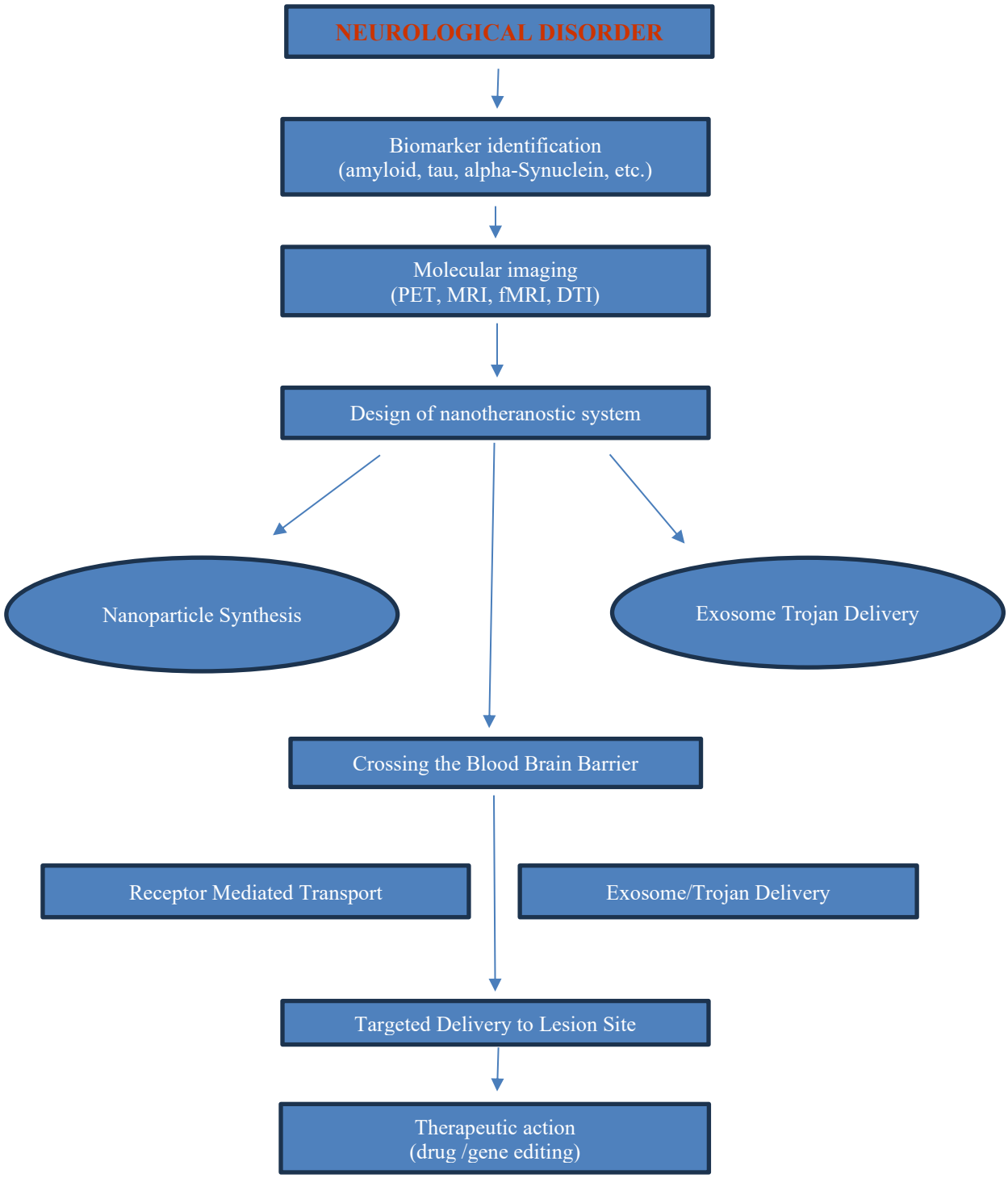

Figure 1: Molecular imaging in neurological theranostics

Positron emission tomography (PET): PET imaging allows for the visualization of pathological protein aggregates in Alzheimer's disease, AD (amyloid-β and tau), and neurochemically disrupted neurotransmission in Parkinson's disease (PD). Amyloid positron emission tomography (PET) is a highly sensitive non-invasive imaging modality for visualizing amyloid-β (Aβ) plaques *in vivo*, a feature of AD. It involves radiolabeled probes that selectively bind to fibrillar Aβ, enabling clinicians and researchers to determine amyloid deposition in the brain with high sensitivity and specificity. This is most useful in the early phases of AD, when clinical symptoms are mild or uncertain [6].

Most frequently used amyloid PET tracers are PiB (Pittsburgh compound B), Florbetapir (Amyvid), Florbetaben (Neuraceq), and Flutemetamol (Vizamyl). Other PET's is Tau-PET aids in the staging of disease progression, and dopaminergic function PET tracers aid in early diagnosis of Parkinsonian syndromes [7, 8].

Magnetic resonance imaging (MRI)-based theranostic approaches: MRI is a non-invasive imaging technique applied in neurological diagnosis because of its excellent soft tissue contrast and spatial resolution. MRI has a dual purpose in theranostics: Facilitating real-time high-resolution anatomical imaging and use as an assessment tool for monitoring therapy delivery and effectiveness. MRI is also augmented with contrast agents such as gadolinium or iron oxide nanoparticles. MRI-guided drug delivery with functionalized nanoparticles (NPs) provides the capacity to visualize simultaneously and deliver localized therapy [9].

Advanced MRI techniques: In addition to conventional imaging, advanced MRI modalities are being combined into theranostic uses: *Diffusion tensor imaging (DTI),* For tracking white matter in neurodegeneration. *functional MRI (fMRI):* To measure functional changes before and after treatment. *Magnetic resonance Spectroscopy (MRS)*: To quantify biochemical changes (NAA, choline, lactate) of therapy response. These technologies, in conjunction with site-specific MRI contrast agents, form a strong theranostic arsenal [10].

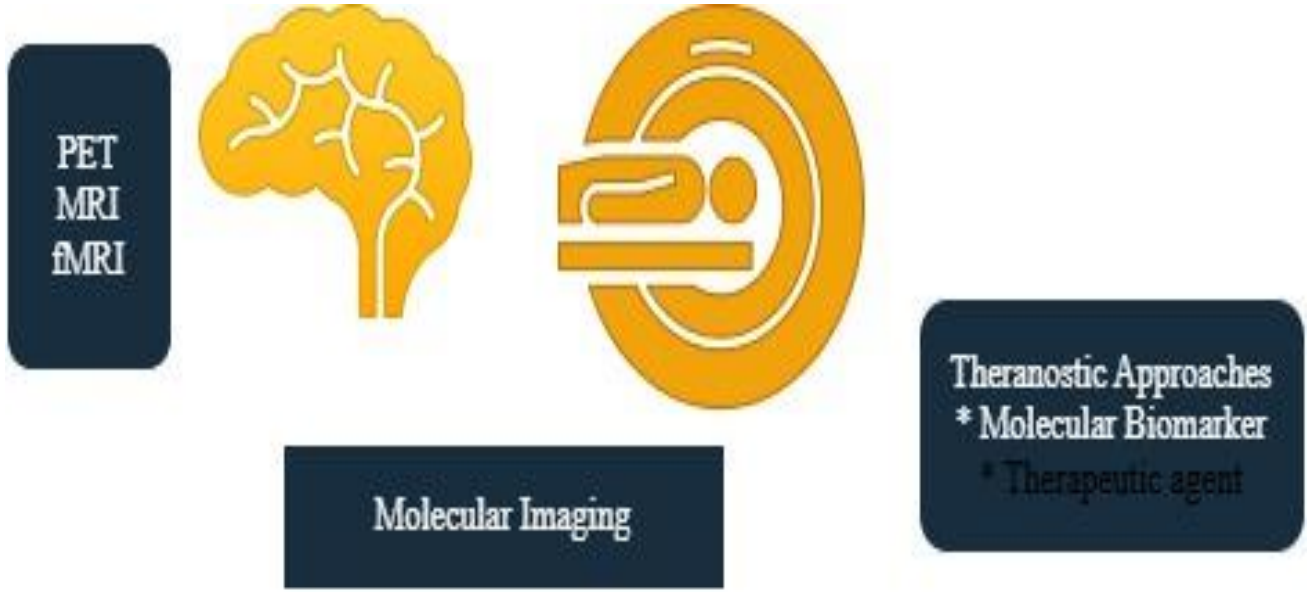

Figure 2: Nanotheranostics and the blood-brain barrier

Nanoparticles for imaging and drug delivery: NPs have distinct physicochemical characteristics, allowing them to penetrate the BBB, deliver therapeutic payload, and serve as imaging probes. Lipid NPs are biocompatible and efficient at encapsulating lipophilic drugs [11]. Polymeric NPs such as PLGA-PEG are employed for delivering anti-inflammatory drugs in MS [12, 13]. Inorganic NPs (iron oxide and gold) provide imaging contrast and therapeutic advantage [14].

Functionalization for penetration of BBB: Surface functionalization with target ligands including transferrin, insulin, or antibodies, increases NPs internalization through receptor-mediated transcytosis [15].

Therapeutic applications in specific neurological diseases

Alzheimer's disease: It is a neurodegenerative disease with progressive loss of memory, cognitive impairment, and behavioral alterations [1]. It is clinically and pathologically marked by the deposition of amyloid-β plaques and neurofibrillary tangles made of hyper phosphorylated tau protein. These molecular features are particular targets for intervention with theranostics. Amyloid PET agents, including [11C]PiB and [18F]florbetapir, allow for imaging of amyloid plaques, whereas tau PET agents like [18F]AV-1451 are employed to track tau pathology and relate to disease severity [16]. Theranostics nanoplatforms for AD generally combine diagnostic agents (MRI contrast NPs or PET tracers) with therapeutic agents like anti-amyloid antibodies, curcumin, or siRNAs. These platforms are intended to decrease plaque burden and offer imaging feedback regarding the efficacy of treatment. For example, curcumin-loaded PLGA NPs have been shown to possess dual functions of amyloid plaque binding and neuroprotection [17]. Besides, multifunctional lipid NPs have been investigated for targeted delivery of anti-tau siRNAs, with lowered tau expression and enhanced cognitive performance in mouse models. Other platforms employ antibody-conjugated nanocarriers that cross the BBB and bind selectively to Aβ plaques, delivering therapeutic and imaging advantages. The intersection of molecular imaging, targeted delivery, and real-time monitoring places theranostics at center stage in the transition towards personalized treatment strategies for AD. Nanotheranostic systems targeting amyloid-β plaques deliver drugs (curcumin, antibodies) and allow real-time tracking via PET or MRI [18]. Early-stage diagnosis with tau-PET combined with therapeutic siRNA delivery has shown promise in preclinical models [19].

Parkinson's disease: It is a progressive, chronic neurological disease caused by the degeneration of dopaminergic neurons in the substantia nigra. Pathogenesis includes oxidative stress, mitochondrial impairment, and α-synuclein aggregation [20]. Lipid-based nanocarriers and exosomes are explored for targeted delivery of neuroprotection agents (Coenzyme Q10, levodopa, siRNA to α-synuclein). Dual-labeled NPs enable concomitant drug delivery and real-time imaging for evaluation of biodistribution and response. Lipid-based NPs and exosomes are being explored as nanocarriers for targeted delivery of neuroprotective drugs (coenzyme Q10, levodopa, siRNA to α-synuclein). Iron oxide NPs conjugated with L-dopa or dopamine agonists and labeled to target dopaminergic neurons and provide imaging by MRI. Preclinically investigated for neuroprotective delivery with real-time monitoring [21].

Multiple sclerosis (MS): MS is an autoimmune nervous system disorder in the CNS. Conventional imaging is useful for monitoring lesion development but does not provide cellular-level detail. Theranostic treatments in MS involve the employment of superparamagnetic iron oxide nanoparticles (SPIONs) that are conjugated with anti-inflammatory cell target antibodies (CD4+ T cells). These enable visualization of active lesions along with targeted delivery of immunomodulatory drugs (fingolimod, corticosteroids) [22]. Nanoplatforms bearing anti-inflammatory peptides or siRNAs are under investigation for their immune activation-suppressing capability and their MRI-detectable signature [23]. Superparamagnetic iron oxide NPs aid in the detection of inflammatory lesions and targeting corticosteroids or monoclonal antibodies to pathological locations [24].

Glioblastoma multiforme (GBM): GBM is a primary brain tumor with an aggressive prognosis. The invasive properties, tumor heterogeneity, and BBB constrain the efficacy of treatment [25]. Recent approaches combine photothermal therapy, chemotherapy, and real-time MRI/PET monitoring, showing promise in both preclinical models and early-phase clinical trials [26]. Theranostic platforms use gold or polymeric NPs targeting EGFR, a surface marker overexpressed in GBM, to deliver chemotherapeutics while enabling CT or MRI imaging [27].

Epilepsy: It is a long-term neurological condition with recurrent seizures caused by abnormal electrical activity in the brain [28]. The condition is extremely heterogeneous and includes several syndromes with varying etiologies such as genetic mutations, traumatic brain injury, infection, and neurodevelopmental abnormalities [29]. Traditional imaging methods such as MRI and CT are unable to identify epileptogenic foci, especially in non-lesional epilepsy. Theranostics mean attempting to break this barrier by combining sophisticated molecular imaging and targeted therapy [30, 31].

Table 1: Examples of nanotheranostic applications targeting the blood-brain barrier

Disease	Theranostic agent	Targeting Strategy	Imaging modality	Therapeutic Payload
Glioblastoma	Transferrin-modified liposomes	Receptor mediated transcytosis	MRI/PET	Temozolomide, siRNA
Alzheimer's	A Beta-antibody conjugated nanoparticles	Active mediated (A Beta-plaques)	MRI/Optical	Curcumin, anti-A beta siRNA
Epilepsy	GABA- Receptor targeted Nanocarriers	Ligand-based targetting	Fluorescence/MRI	Carbamazepine
Parkinson's	Exosome-encapsulated CRISPR-CAS9	Trojan horse (Exosomes)	MRI	Alpha-synuclein gene editing

Theranostics techniques in epilepsy

Molecular imaging: PET tracers including [^{11}C]flumazenil (for $GABA_A$ receptor binding) and [^{18}F]FDG for glucose metabolism, localize seizure foci more precisely to define areas of cortical hypometabolism related to epileptic activity [32].

Targeted nanocarriers: Anticonvulsant-loaded NPs (valproic acid, carbamazepine) coated with ligands against inflammatory or neurotransmitter-related receptors can penetrate the BBB and target drugs to hyperexcitable neurons. Certain systems also incorporate fluorescent or MRI-readable tags for imaging guidance. Theranostics has the potential to improve seizure focus localization, customized drug delivery, and real-time monitoring, particularly for drug-resistant or surgically intractable epilepsy cases [33].

CRISPR-Cas9 Theranostics: It is a groundbreaking genome-editing technology that provides for the targeting and alteration of DNA sequences with high precision. Theranostics utilize this technology more and more, not just for gene repair but also for diagnosis, so that treatment and diagnosis can be pursued in tandem in neurological disease [34]. Gene-editing platforms embedded in nanocarriers are being investigated for inherited neurological diseases like Huntington's disease [35, 36].

Ultrasound-triggered system: Focused ultrasound combined with microbubbles temporarily disrupts the BBB, allowing controlled drug release [37].

Artificial intelligence in theranostics: Machine learning in algorithms analyzes multimodal imaging and clinical data to personalize theranostics strategies [38, 39].

Translational and clinical challenges

Blood-brain barrier penetration: As yet, safe and effective delivery through the BBB is a challenge despite the progress [40]. *Safety and toxicity:* There is no complete proof of long-term biocompatibility of NPs. *Regulatory pathways:* Theranostic agents' approval is burdened by complex regulations due to dual-functionality. *Cost:* Production and development expenses are high, making scalability impossible [41].

Table 2: Common theranostic agents in neurology

Agent type	Target disease	Diagnostic modality	Therapeutic function
Iron oxide nanoparticles	Glioblastoma, MS	MRI	Drug delivery, imaging contrast
Radiolabeled tracers ([18F]florbetapir)	Alzheimer's Disease	PET	Diagnostic imaging
Gold nanoparticles	Glioblastoma	CT, MRI	Chemotherapy delivery, photothermal therapy
Polymeric nanoparticles (PLGA-PEG)	Multiple Sclerosis	MRI	Anti-inflammatory drug delivery
Lipid nanoparticles	Parkinson's Disease	MRI	Neuroprotective agent delivery

Conclusion: Theranostics in neurology offers a transformative approach to managing complex brain diseases. By enabling simultaneous diagnosis, targeted treatment, and real-time monitoring, theranostic platforms embody the ideals of precision medicine. Continued interdisciplinary research and the integration of artificial intelligence, nanotechnology, and advanced imaging will be essential to overcome translational challenges and unlock clinical potential. Looking ahead, the integration of emerging technologies such as artificial intelligence, advanced biomaterials, and gene-editing techniques will further propel the theranostic field. Personalized medicine will benefit from enhanced biomarker discovery, multimodal imaging, and precise spatiotemporal control of therapeutic delivery.

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